Proposed Decision Memo for Positron Emission Tomography for Initial Treatment Strategy in Solid Tumors and Myeloma (CAG-00181R3)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) was asked to reconsider the April 3, 2009 NCD provision at Section 220.6.17 of the National Coverage Determinations (NCD) Manual, described below, that established an absolute frequency limitation of only one FDG PET study for the noted purposes.

"CMS will cover only one FDG PET study for beneficiaries who have solid tumors that are biopsy proven or strongly suspected based on other diagnostic testing when the beneficiary's treating physician determines that the FDG PET study is needed to determine the location and/or extent of the tumor for the following therapeutic purposes related to the initial treatment strategy:

- To determine whether or not the beneficiary is an appropriate candidate for an invasive diagnostic or therapeutic procedure; or
- To determine the optimal anatomic location for an invasive procedure; or
- To determine the anatomic extent of tumor when the recommended anti-tumor treatment reasonably depends on the extent of the tumor."

After careful review, CMS believes that the current absolute restriction is not supported by the available evidence and therefore proposes to amend 220.6.17 of the National Coverage Determinations Manual:

1. the NCD will be changed to remove the current absolute restriction of coverage to 'only one' FDG PET scan to determine the location and/or extent of the tumor for the therapeutic purposes related to the initial treatment strategy as described above;
2. CMS will continue to nationally cover one FDG PET scan to determine the location and/or extent of the tumor for the therapeutic purposes related to the initial treatment strategy as described above; and

3. local Medicare administrative contractors will have discretion to cover (or not cover) within their jurisdictions any additional FDG PET scan for the therapeutic purposes related to the initial treatment strategy as described above.

For any individual beneficiary the usefulness of any additional FDG PET scan for initial treatment planning might be affected by the beneficiary's specific medical problem, the availability of results of other diagnostic tests and the expertise of the interpreting physician. We believe in such situations that our local administrative contractors, who may more readily obtain this information, can make these determinations about any additional FDG PET scan for initial treatment planning within their jurisdictions. We do not believe that a national coverage determination is the most appropriate way to address coverage for any additional FDG PET scans for the therapeutic purposes related to the initial treatment strategy at this time.

We are requesting public comments on this proposed decision memorandum pursuant to §1862(l)(3) of the Social Security Act (hereinafter, the Act). We are particularly interested in comments that include new evidence we have not reviewed here or in past considerations of this NCD. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

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SUBJECT: Request for Reconsideration of Positron Emission Tomography for Solid Tumors and Myeloma (CAG-00181R3)

DATE: May 6, 2010

I. Proposed Decision

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II. Background

Throughout this memorandum, we use the term FDG to refer to 2-deoxy-2-[F-18] fluoro-D-glucose, also known as F-18 fluorodeoxyglucose. We use the term PET to refer to positron emission tomography or to a positron emission tomogram, depending on context. The term FDG PET refers to PET imaging utilizing FDG as the radioactive tracer, and in the context of this document, includes the use of combined or integrated positron emission tomography/computed tomography using FDG as the radioactive tracer (FDG PET/CT). We use the abbreviation MBq to denote megabecquerel, a unit of radioactivity in the International System of Units (SI). We use the term gray (abbreviated Gy) as the unit of therapeutic radiation dose, defined as one joule of energy in the form of X-rays or gamma rays absorbed by one kilogram of mass. The centigray (cGy) is an alternate form of this unit used by some authors and is defined as 0.01 Gy. We use the abbreviation TNM to denote the dimensions of malignant tumor spread within a given patient, as defined by the American Joint Committee on Cancer and as used by National Cancer Institute, other clinical standards organizations and healthcare providers.

FDG PET is a minimally-invasive diagnostic imaging procedure used to evaluate glucose metabolism in normal tissue as well as in diseased tissues in conditions such as cancer, ischemic heart disease, and some neurologic disorders. FDG is an injected radioactive tracer substance (radionuclide) that emits sub-atomic particles, known as positrons, as it decays. FDG PET uses a positron camera (tomograph) to measure the decay of radioisotopes such as FDG. The rate of FDG decay provides biochemical information on glucose metabolism in the tissue being studied. As malignancies can cause abnormalities of metabolism and blood flow, FDG PET evaluation may indicate the probable presence or absence of a malignancy based upon observed differences in biologic activity compared to adjacent tissues.

Other forms of diagnostic imaging technologies such as x-ray imaging, computed tomography (CT), and magnetic resonance imaging (MRI) supply information about the anatomic structure of suspected malignancies, primarily their size and location. However, clinical imaging of glucose metabolism within cells is unique to FDG PET technology. In many cases, the anatomical information provided by CT or MRI is most important in devising a treatment strategy. However, the metabolic information provided by FDG PET imaging may provide complementary information that is helpful in determining the initial treatment.

Successful external RT for control of malignant solid tumors depends on delivery of sufficient ionizing radiation to the clinical target volume (the detectable tumor plus a margin for microscopic extension). Ideally, the clinical target volume closely conforms to the tumor contour. Accurate delineation of clinical target volume leads to a greater fraction of radiation dose being delivered to tumor tissue, and less radiation delivered to surrounding uninvolved tissue which may experience radiation toxicity. However, incorrect delineation of the gross target volume may lead to undertreatment, and reducing the possibility of tumor control while increasing the risk of adverse radiation exposure (see for example, Senan and DeRuysscher 2005).

FDG PET imaging techniques are thought to contribute to the accuracy of RT planning by delineating the ‘glucose-avid’ extent of malignant tumors, and thereby providing complementary information to that provided by other techniques (such as CT) which depend on tissue structure and/or radiodensity. FDG PET, by revealing unsuspected distant metastases, can change treatment strategy, as acknowledged in prior national coverage determinations (see, for example, CMS 2009). Although studies of survival after radiotherapy have reported superior results in patients who have undergone a staging PET scan, some authors attribute these improved results in part to the exclusion from curative RT efforts of ~ 20% of patients revealed by PET scan to have distant metastases not previously known (for example, MacManus et al., 2001). In this 2001 case series study, staging FDG-PET was performed for 167 patients with Stage I–III non small-cell lung cancer (NSCLC) by conventional workup. These patients were candidates for curative therapy with surgery, radical chemo/RT or RT, or preoperative chemo/RT. In 32/167 patients (19%), PET detected distant metastases, most commonly (in 17/32 patients) abdominal (including adrenal and liver) metastases.

For solid epithelial tumors, therapeutic radiation doses often reach 60-80 Gy; for lymphomas, lower levels (20-40 Gy) of radiation may be effective. Some authors have suggested that, given that with such regimens, substantial local failure rates and poor 5-year survival, studies of escalating radiation dose are called for (Gillham et al., 2008). RT dose regimens including such 'boost' strategies will be even more dependent on accurate tumor size and positioning information to guide treatment plans.

III. History of Medicare Coverage

Positron emission tomography (PET) is a noninvasive diagnostic imaging procedure that assesses the level of metabolic activity and perfusion in various organ systems of the body. A positron camera (tomograph) is used to produce cross-sectional tomographic images, which are obtained from positron emitting radioactive tracer substances (radiopharmaceuticals) such as 2-[F-18] Fluoro-D-Glucose (FDG), that are administered intravenously to the patient. Radiopharmaceutical diagnostic imaging agents in PET cancer imaging other than 2-[F-18] Fluoro-D-Glucose (FDG) and NaF-18 (sodium fluoride-18) are noncovered by Medicare.

A. Current Request

CMS was asked to reconsider the provisions of Section 220.6.17 of the NCD Manual to remove the restriction that only one FDG PET scan may be performed as part of guiding initial antitumor treatment strategy of solid tumors and myeloma. In 2009, CMS covered the use of FDG PET/CT scans during initial treatment strategy planning in recognition of its value in clarifying tumor stage or burden and in preventing unnecessary treatment. In this 2009 decision, CMS indicated that only one FDG PET/CT would be covered during initial antitumor treatment strategy. It is this aspect of that decision (CMS 2009) which the requestors have brought up for reconsideration in a letter to CMS of October 14, 2009. The requestors supplemented this letter with a public comment submitted to CMS on December 9, 2009, indicating several additional citations.

In the October 14, 2009 letter, submitted on behalf of the National Oncologic PET Registry (NOPR) Working Group, The Academy of Molecular Imaging (AMI), the American College of Nuclear Medicine (ACNM), the American College of Radiology (ACR), the American Society for Radiation Oncology (ASTRO), and the Society of Nuclear Medicine (SNM), the requestors indicated that:

"We collectively and strongly support the approach taken by CMS in CAG-OOI81R to streamline the FDG-PET coverage framework into "initial" and "subsequent" treatment strategy evaluation, as we believe that this is a positive development for providers, patients, and payors. However, we remain concerned that the failure of CMS to acknowledge the need for clinically necessary "later initial" scans in certain limited clinical situations may hamper good clinical practice. In response to comments encouraging coverage for later initial scans in such situations, CMS stated that the evidence it had reviewed "addressed the use of single scans," and that "coverage as we have described of only one FDG-PET scan to guide initial antitumor treatment is consistent with the current evidence base." The new NCD, in section IX(2) (Initial Antitumor Treatment Strategy),articulates the formal policy as follows (emphasis supplied):

CMS has determined that the evidence is adequate to determine that the results of FDG PET imaging are useful in determining the appropriate initial treatment strategy for beneficiaries with suspected solid tumors and myeloma and improve health outcomes and thus are reasonable and necessary under §1862(a)(l)(A) of the Social Security Act. Therefore, CMS will cover *only one* FDG PET study for beneficiaries who have solid tumors that are biopsy proven or strongly suspected based on other diagnostic testing when the beneficiary's treating physician determines that the FDG PET study is needed to determine the location and/or extent of the tumor for the following therapeutic purposes related to the initial treatment strategy:

- To determine whether or not the beneficiary is an appropriate candidate for an invasive diagnostic or therapeutic procedure; or
- To determine the optimal anatomic location for an invasive procedure; or
- To determine the anatomic extent of tumor when the recommended anti-tumor treatment reasonably depends on the extent of the tumor."

"Three practical scenarios illustrate our general concern with the bright-line approach taken in CAG-OO 181 R. First, where PET is used for diagnosis or initial staging purposes, the result may indicate that radiation therapy, rather than surgery, is the appropriate method of treatment. In such situations, a second (initial) PET scan, often a limited study done under technically different conditions, may be needed for radiation therapy planning (e.g., for PET based simulation). Second, in a small fraction of patients, PET used to evaluate a suspicious lesion (e.g., a pulmonary nodule) for cancer diagnosis can produce a false-negative result. If such patients are subsequently diagnosed with cancer, however, the prevailing standard of care is to use PET for initial staging prior to treatment, in order to obviate futile locally directed treatment (surgery or definitive radiation therapy) in those patients who had developed metastatic disease in the interval. Third, in some patients with newly diagnosed cancer staged by an initial PET scan, definitive treatment may be delayed either because of patient reluctance or because of intercurrent medical illness that must first be addressed (e.g., a patient who must undergo coronary artery bypass grafting for multivessel coronary artery disease before a radical cystectomy can be performed for muscle-invasive bladder carcinoma. Again, as in the second example, a second PET scan to document that the disease has not become unresectable may be medically necessary."

B. Benefit Category

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage and not be statutorily excluded. §1812 (Scope of Part A); §1832 (Scope of Part B) and §1861(s) (Definition of Medical and Other Health Services) of the Act. FDG PET falls within the following benefit category: other diagnostic tests as defined in §1861(s)(3) of the Act.

Medicare regulations at 42 C.F.R. § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem."

IV. Timeline of Recent Activities

November 9, 2009	CMS accepted the formal request and posted a tracking sheet on the website, which began the initial 30-day public comment period.
December 9, 2009	The initial 30-day comment period ended. Thirty-five timely comments were received.

V. Food and Drug Administration (FDA) Status

The FDA described the safety and effectiveness findings for FDG F-18 in a Federal Register notice dated March 10, 2000 (Volume 65, Number 48) Notices. Pages 12999-13010:

"The [FDA] Commissioner has concluded that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in FDG PET imaging in patients with coronary artery disease CAD and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function, as discussed in section III.A.1 and III.A.2 of this document. The Commissioner also has concluded that FDG F 18 injection, when produced under the conditions specified in an approved application, can be found to be safe and effective in FDG PET imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer, as discussed in section III.A.1 and III.A.3 of this document. In addition, manufacturers of FDG F 18 injection and sodium fluoride F 18 injection may rely on prior agency determinations of the safety and effectiveness of these drugs for certain epilepsy-related and bone imaging indications, respectively, in submitting either 505(b)(2) applications or amended new drug applications ANDAs for these drugs and indications."

VI. General Methodological Principles

When making NCDs, CMS evaluates relevant clinical evidence to determine whether or not the evidence supports a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for Medicare beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary under § 1862(a)(1)(A) of the Act.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review.

As noted above, with respect to diagnostic tests, the Medicare regulations at 42 CFR § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, we looked for evidence that the additional FDG PET imaging is used by the beneficiary's treating physician in the management of the patient, and the effect of this use on health outcomes.

The requestors presented three clinical scenarios as examples of the need for a 'later initial' FDG PET/CT scan during the initial treatment strategy evaluation period:

1. For radiation therapy planning, any additional FDG PET scan for initial treatment planning may be needed, done under technically different conditions. Examples would include RT planning done at a different institution; RT planning FDG PET that required different patient positioning, e.g., with the patient in the treatment position; or concern for RT planning based on unfavorable patient positioning;
2. Patients with a prior false-negative diagnostic PET scans in whom a cancer is subsequently diagnosed may need any additional FDG PET scan for initial treatment planning for initial staging; and
3. Delay between initial diagnosis and definitive therapy due to various causes (patient reluctance, treatment of a more urgent comorbid condition) requiring any additional FDG PET scan for initial treatment planning to determine whether a change has occurred in tumor size, location, spread, etc.

The requestors contended that there is evidence to support their concern that failure to perform any additional FDG PET scan for initial treatment planning PET scan in any of the above situations is contrary to good medical practice. As evidence for this contention, the requestors cited the results of a number of published clinical studies:

1. Articles about the current standard-of-care for radiation therapy planning (Fraass et al., 1998, Mutic et al., 2003), especially the need for patient positioning (with immobilization) in the treatment position (MacManus 2009);
2. Articles providing large, prospective institutional cohort studies supporting treatment-dedicated FDG PET for RT planning (e.g., Kruser et al., 2009);
3. An article about a United Kingdom health technology assessment report (Facey et al., 2007) concluded that, for non-small cell lung cancers, incorporation of FDG PET imaging results in a 42% pooled weighted average for radiotherapy management changes; and
4. Articles suggesting that the quality of treatment planning is degraded in the absence of treatment-position FDG PET imaging (Hwang et al., 2009).

B. Discussion of evidence reviewed

1. Questions

a. *Is the evidence adequate to conclude that the use of any additional FDG PET scan for initial treatment planning will meaningfully alter the recommended treatment strategy for beneficiaries who have a diagnosis of solid tumors or multiple myeloma?*
b. *Is the evidence adequate to conclude that the use of any additional FDG PET scan for initial treatment planning for radiation therapy planning will meaningfully alter health outcomes for beneficiaries who have a diagnosis of solid tumors or multiple myeloma?*

As a diagnostic test, FDG PET would not be expected to directly change health outcomes, i.e. there is no evidence that the administration of FDG is therapeutic for cancer in and of itself. Rather, a diagnostic test affects health outcomes through changes in disease management brought about by physician actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available treatment options.

Outcomes of interest for a diagnostic test are not limited to determining its accuracy but also include beneficial or adverse clinical effects, such as changes in management due to test findings or preferably, improved health outcomes for Medicare beneficiaries. Ideally, we would see evidence that the systematic incorporation of FDG PET results into treatment decisions leads physicians to prescribe different treatment than they would otherwise have prescribed, and that those patients whose treatment is changed by test results achieve improved outcomes.

2. External Technology Assessments

CMS did not request an external technology assessment (TA) on this issue.

3. Internal technology assessment

CMS reviewed the 30 cited published reports supplied by the requestors, as well as several additional citations submitted by public commenters during the initial public comment period.

CMS also reviewed the published medical literature (using a PubMED search) for articles published since January 2005 with the search terms ‘FDG PET’ and ‘radiation therapy’. Six articles were returned by the search. One article (Hutchings et al., 2007) had also been included with the requestor’s letter, and is reviewed below. One other article (Ortholan et al., 2009 [PMID 18565687]) was not reviewed because it did not study a subsequent FDG PET scan’s impact on RT planning. CMS has reviewed the other four citations (Grgic et al., 2003; Hentschel et al., 2009; Onal et al., 2009; and Waaijer et al., 2003) as full text articles below.

Article summaries below are listed alphabetically within study design categories hierarchy of evidence (See Appendix A).

Technology Assessments:

Facey et al., 2007

In this Health Technology Assessment (HTA) from the National Health Service of the United Kingdom, the authors primarily studied the cost effectiveness of FDG PET scanning for patients with primary or recurrent cancer. The authors based this assessment on a systematic review of the literature for eight tumor types, including breast, colorectal, head and neck, lung, lymphoma, melanoma, esophageal and thyroid. Although the HTA considered studies about the effectiveness of FDG PET scans in various cancer management decisions, including: diagnosis (detection of cancer before confirmation of disease); staging (occurs after histological confirmation and before initial therapy); recurrence (detection of malignancy in followup after disease-free period, often when suspicion is raised by other follow-up tests); restaging (occurs after initial therapy or when recurrence has been confirmed); assessment of treatment response (during or immediately after therapy); and RT planning (before RT to plan target volume and dose); only the final assessment about FDG PET in RT planning was considered germane to this (narrowly focused) reconsideration request.

For these eight tumor types, the investigators also looked at studies about how FDG PET scans aided management decisions in a number of areas including (RT planning. 17 ‘small’ studies were found relating to RT planning for four of these eight tumor types. Although the HTA concluded that FDG PET scans led to alteration of RT volumes and doses, impact on patient outcomes was rarely studied.

The authors of the HTA discussed the evidence as follows:

"The use of FDG-PET to supplement CT or MRI for RT planning is a topic of interest in the FDG PET community. The literature search retrieved 17 primary studies (mainly evaluating replacement of CT before radical RT) in: colorectal cancer (one study); head and neck cancer (three studies of PET and three of PET/CT); NSCLC (eight studies) and oesophageal cancer (two studies).

"The studies were small and used different methods to determine the treatment volume. Review of these studies suggests that it would be helpful to establish consensus standards for translating FDG PET images into volumes for use in RT planning, to promote consistency across future studies and reproducibility in clinical practice. Only one study provided any outcome data,[123] evaluating nodal failure outside the radiation field after 16 months' follow-up in NSCLC. Collection of such outcome data should be encouraged and optimally RCTs should be performed to demonstrate definitively the added value of FDG PET/CT in RT planning."

The authors commented that larger studies of impact of FDG PET would be needed.

Prospective Case-Control Studies:

Kidd et al., 2009

In this prospective study of a consecutive series of 452 patients with newly diagnosed cervical cancer treated with curative intent with definitive IMRT, the authors compared the toxicity and clinical outcomes for 135 patients treated definitively with intensity-modulated radiation therapy (IMRT) during or after March 2005 against the same outcomes in 317 patients with non-IMRT (before March 2005) treatment. All IMRT patients underwent an F-18 fluorodeoxyglucose positron emission tomography (FDG-PET/CT) simulation. Pretreatment staging workup included either whole-body FDG PET or FDG PET/CT; after completing radiation treatment, a repeat PET or PET/CT was performed to evaluate response and any residual or progressive disease. Treatment involved external irradiation and brachytherapy, and 85% of patients received concurrent chemotherapy. Toxicity was scored by the Common Terminology Criteria for Adverse Events Version 3.0. The authors found that the IMRT and non-IMRT groups had similar stage distribution and histology. For all patients, the post-therapy FDG-PET response correlated with overall recurrence risk ($p < 0.0001$) and cause-specific survival ($p < 0.0001$). Post-treatment FDG-PET findings were not significantly different between the IMRT and non- IMRT patients ($p = 0.9774$). The mean follow-up for all patients alive at the time of last follow-up was 52 months (72 months non-IMRT, 22 months IMRT). At last follow-up, 178 patients (39/135 (29%) IMRT, 139/317 (44%) non-IMRT) had developed a recurrence. The difference in recurrence-free survival between the two groups did not reach statistical significance ($p = 0.0738$), although the IMRT group showed better overall and cause-specific survivals ($p < 0.0001$). Of the patients, 62 patients (8/135 (6%) IMRT and 54/317 (17%) non-IMRT) developed Grade 3 or greater bowel or bladder complications, and by cumulative hazard function analysis the risk was significantly less for patients treated with IMRT ($p = 0.0351$). The authors concluded that cervical cancer patients treated with FDG-PET/CT-guided IMRT have improved survival and less treatment-related toxicity compared with patients treated with non-IMRT radiotherapy.

Prospective Case Series Studies:

Anderson et al., 2007

In this prospective case series study, the authors compare between gross tumor volume (GTV) and planning tumor volume (PTV), measured in cubic centimeters, based on either CT simulation or FDG PET studies. Patients included thirteen men and ten women, with mean age of 58 years, ranging from 30-81 years. Twenty patients were treated for rectal cancer, and three patients were treated for anal cancer. The degree of overlap of these volumes (OV) for each method was based on manual image registration. Patients were treated with conformal therapy using traditional doses. The average OV was 46%, ranging from 11% to 99%. On average, PET-GTV was smaller than mean CT-GTV (91.7 (range 2.9 – 859) cm^3) v. 99.6 (range 17-570) cm^3). Management was changed (predominantly by avoiding unnecessary surgery and early detection of distant metastases) in 25% of patients with rectal cancer, in whom PET studies detected distant metastases. Four of 23 (17%) of patients had changes in the PTV when FDG PET findings were included. The authors suggested that the advantage of FDG PET imaging was the avidity of tumors for glucose, allowing sharper demarcation of tumor volume, than with CT alone, and recommended use of PET-CT for initial staging and workup of anorectal tumors for radiation therapy planning.

De Ruysscher et al., 2005

In this prospective case series study of 21 patients with locally advanced non-small cell lung cancers (NSCLC), conformal radiation therapy planning was studied using a combined PET-CT simulator. Patients in this study had pathologically proven NSCLC, without distant metastases by PET scan. Patient demographic characteristics were not provided. For each patient, two 3D conformal treatment plans were made; one with CT based PTV, and one with PET-CT based PTV, both plans designed to deliver 60 Gy in 30 fractions. Protection of lung, esophageal, and spinal cord fields was attempted by minimizing their exposure. In these patients, addition of PET information for calculating dose delivery increased the dose from 55.2 Gy +/- 2 Gy (CT planning) to 68.9 +/- 3.3 Gy (PET-CT planning), without increasing the toxicity to lung, esophagus, and spinal cord. The estimated Tumor Control Probability was estimated to be significantly increased with PET-CT planning, from 6.3 +/- 1.5% for CT planning to 24.0 +/- 5.0% with PET-CT planning ($p = 0.01$). The authors noted that a limitation of the study was the unavoidable motion of the chest during respiration, which might compromise the precision of both imaging for RT planning and dose delivery.

De Ruysscher et al., 2005B

In this prospective study (cited by Facey et al., 2007 as noted above) involving 44 patients with histologically proven NSCLC without detectable distant metastases, the authors investigated the occurrence of isolated nodal failure (i.e., recurrence of tumor in the regional nodes outside the clinical target volume), in the absence of in-field failure. Patients included 27 males and 17 females, with patients' ages ranging from 51 to 89 years, with a median age of 68 years. Mediastinal irradiation was performed if FDG PET scans demonstrated activity in that region. After a median post-RT followup of 16 months (CI 11-21 months), eleven of 44 (25%) of study patients developed a local recurrence. One of eleven patients developed an isolated node failure; five failed in the primary RT tumor volume; and five failed within and distant to the primary RT tumor volume. The authors concluded that selective mediastinal node irradiation based on FDG PET scan data results in low isolated nodal failure rates in NSCLC. The authors also noted that toxicity to lung, esophagus and spinal cord were known adverse effects of mediastinal irradiation, and that FDG PET study results may be subject to inaccuracy.

Ford et al., 2008

This prospective study examine the impact of PET-CT scanning to determine RT target volume in 12 women who were candidates for partial breast irradiation (PBI) to the lumpectomy cavity (LC) following lumpectomy for breast cancer. Inclusion criteria were: primary breast cancer no more than 4 cm in diameter; zero to three positive axillary lymph nodes; at least 3 mm negative lumpectomy margins; and plans to receive chemotherapy. Patient demographics were not provided in the article. Within a median of 49 (range 24-67) days after lumpectomy surgery, the patients underwent a PET-CT scan. Patients also underwent a treatment planning CT scan, using the same setup and immobilization as for the PET-CT scan. For most patients, the PET-CT and planning CT were performed on the same day; the remainder had both scans performed within the same week. Registration of PET-CT and planning CT was accomplished manually using software landmarks by a study radiation oncologist and nuclear medicine physician with knowledge of both PET-CT and planning CT scan results. Treatment began within 1-1.5 weeks of the scans for the 'vast majority of patients'. The authors believed that any changes in the cavities between the completion of the scans and the start of RT were minimal. Results showed that the volumes of the PET-CT contours of the LC were greater than those determined by planning CT. The median difference between the LC volumes was 14.7 (1.8-65.9) cm^3. The PET-CT and planning CT LC volumes were described as 'well correlated'. The authors acknowledged the absence of a reference technique to quantitate LC volume. The authors also commented that the increased FDG uptake around the rim of the LC was likely because of postoperative inflammation. In 9 of 12 patients, a CT-based treatment plan did not provide adequate coverage of the PET/CT-based PTV (99% of the PTV received <95% of the prescribed dose), resulting in substantial cold spots in some plans. In these cases, treatment plans were generated which were specifically designed to cover the larger PET/CT-based PTV. The authors commented that a 'potential disadvantage of PET-CT-based RT plans is that the dose to the normal tissue structures might increase…". Although these plans showed an increased dose to the normal tissues, the increases were 'modest': the non–target breast volume receiving ≥ 50 Gy, lung volume receiving ≥ 30 Gy and heart volume receiving ≥ 20 Gy increased by 5.7%, 0.8%, and 0.2%, respectively. The authors concluded that FDG-PET/CT can be used to define the LC volume with only a modest increase in irradiated tissue volume compared with CT-determined PTVs. They suggested that their results should be evaluated in a larger population.

Gillham et al., 2008

In this prospective study, the authors evaluated the use of an additional PET-CT scan in 10 patients with NSCLC at week 5-6 of radiotherapy. The study was designed to test the hypothesis that a reduction in disease volume during radiotherapy detected by FDG PET/CT would facilitate radiation dose escalation, whilst remaining within normal tissue constraints. The ten patients included 2 females and 8 males, with average age of 66 years (range: 51-83 years), and including stages: any T, any N, and M0, with no prior radiotherapy; however, seven patients received prior chemotherapy prior to enrollment. Each received standard 3D-conformally planned radiotherapy to a dose of 66 Gy in 33 fractions over 6.5 weeks. FDG PET/CT imaging in the treatment position was performed twice: once prior to treatment and then repeated following 50 or 60 Gy of radiotherapy. Based on the later PET-CT at 5-6 weeks of radiotherapy, there was a median PTV reduction after 50/60 Gy from 66 (range 12-324) cm^3 to 45 (range 0-162) cm^3, with a median percent reduction of 43%. The delivery of 78 Gy was feasible in 4 of 10 patients; in the remaining 6 patients, radiation dose to the lung or esophagus would have exceeded the individualized dose prescription indicated a higher median maximal dose when treatment would be given in two phases compared to one phase resulting in a modest increase of calculated tumor control probability. However, the authors concluded that, despite tumor shrinkage determined by subsequent FDG PET/CT during treatment, adaptive targeting strategy would result only in a modest improvement in the context of dose escalation, and indicated that further studies of this technique are warranted.

Hentschel et al., 2009

In this prospective, two-center study of 27 patients with histologically proven primary head and neck cancer (HNC) who were treated with combined chemoradiotherapy (CRT) for intended cure, the investigators studied how results of multiple FDG PET scans changed over time, including standardized uptake value (SUV) and gross tumor volume (GTV-PET) and metabolic volume (MV). Patients ranged in age from 44 to 70 years of age, with a median age of 54.2 years. 20 males and three females were included in this study, with primary tumor sites in the oropharynx (twelve tumors (52%)), hypopharynx (ten (44%)), and lip and oral cavity (one (4%)). Before or during the RT treatment of six weeks' duration, every patient underwent four PET/CT scans, one initial scan (before RT) and three PET/CT scans during RT (at end of $1^{st}/2^{nd}$ week, end of $3^{rd}/4^{th}$ week, and end of $5^{th}/6^{th}$ week) using a plastic facemask to ensure patient positioning in the treatment position. All patient FDG PET scans were performed beginning within 50-70 minutes of infusion of 259-341 MBq of FDG. FDG PET data from all scans were analyzed to assess multiple parameters: maximum and mean SUV; PET-based GTV (GTV-PET); and MV, which was calculated as mean SUV multiplied by GTV-PET and, according to the authors, is believed to describe 'total lesion glycolysis'. Results showed that median SUV for the whole population decreased continuously during the course of RT from a median initial (pre-RT) value of 15.2 to a late therapy values ($5^{th}/6^{th}$ week) of 6.4. In contrast, median GTV-PET for the whole population increased from 9.3 cm^3 to 17.9 cm^3, while median MV decreased from 92.2 to 71.3 cm^3. The authors concluded that increased GTV-PET was due, not to increased tumor volume, but to glucose-avid inflammation of surrounding tissue. They suggested further research into other [18]F labeled tracers which would avoid this problem and allow for adaptive radiotherapy, changing during the course of treatments.

Hutchings et al. 2007

This prospective study of 30 patients with early-stage Hodgkin lymphoma (HL) examined the effect of the radiation therapy plan of using CT results from an initial staging FDG PET-CT scan, compared with the effect of a later FDG-PET/CT scan for RT planning. Patients with diabetes mellitus, pregnancy, and those younger than 18 years were excluded. Patients included 16 females and 14 males, and the average patient age was 40.2 (range 18.6-79.2) years. Ten patients were Stage I by conventional staging; 20 patients were Stage II. One of thirty patients had extranodal disease. Ten of 30 patients had bulky disease. 60% of patients had nodular sclerosing HL. Twenty-five of 30 patients initially received ABVD chemotherapy; 2 received ABVD/MOPP chemotherapy; while 3 received radiotherapy only. Twenty-nine of 30 patients were in complete remission after a median followup of 24 months. The authors noted that in 20 of 30 patients, FDG-PET/CT did not change the tumor delineation notably, and they suggested that the RT plan would not have been affected by PET/CT. However, in 10/30 patients, FDG-PET/CT results did lead to modification of the radiation fields, leading in 7/10 cases to an increased target volume for irradiation. In one case among these 10, FDG-PET/CT for RT planning identified a distant FDG-avid site, leading to upstaging (from Stage II to III) and a change in treatment strategy. Based on this series, the authors conclude that "… It is therefore not advisable to apply FDG-PETCT to the RT planning procedures alone, but rather to take advantage of the greater accuracy of the anatomic definition of lymphoma involvement and reduce treatment volumes."

Kruser et al., 2009

In this prospective, blinded trial, the authors prospectively examined the impact of hybrid PET/CT imaging on overall oncologic impact, with a focus on radiotherapy planning. 111 patients, including patients with lung cancer (n=38), head-and-neck squamous cell carcinoma (n=23), breast (n=8), cervix (n=15), esophageal (n=9), and lymphoma (n=18) underwent hybrid PET/CT imaging at the time of radiation therapy planning. A physician blinded to the PET dataset designed a treatment plan using all clinical information and the CT dataset. The treating physician subsequently designed a second treatment plan using the hybrid PET/CT dataset. The two treatment plans were compared to determine if a major alteration in overall oncologic management occurred. In patients receiving potentially curative radiotherapy the concordance between CT-based and PET/CT-based GTVs was quantified using an index of conformality (CI). In 76/111 (68%) of patients, the PET/CT data resulted in a change in one or more of the following: GTV volume, regional/local extension, prescribed dose, or treatment modality selection. In 35 of these 76 cases (46%; 31.5% of the entire cohort) the change resulted in a major alteration in the oncologic management (dose, field design, or modality change). Thus, nearly a third of all cases had a major alteration in oncologic management as a result of the PET/CT data, and 29 of 105 patients (27.6%) who underwent potentially curative radiotherapy had major alterations in either dose or field design. Hybrid PET/CT imaging at the time of treatment planning may be highly informative and an economical manner in which to obtain PET imaging, with the dual goals of staging and treatment planning.

Onal et al., 2009

In this study of 52 patients with histologically proven prostate cancer treated with three dimensional conformal radiotherapy (3D-CRT), the authors investigated the effect on prostate volume from concurrent 3D-CRT and androgen deprivation (AD) due to concerns that shifts in tumor volume might increased RT dose delivered to adjacent bowel, bladder and bone. Patients' ages ranged from 63-76 years, with a median age of 71 years. Before RT began, all patients received at least 3 months' treatment with a combination of goserelin and bicalutamide. [CMS note (source: FDA prescribing information): Goserelin is a synthetic analogue of naturally occurring luteinizing hormone releasing hormone (LHRH). Chronic goserelin administration "… results in inhibition of pituitary LH secretion leading to a fall in serum testosterone concentrations in males(.) … In men by around 21 days after the first depot injection, testosterone concentrations have fallen to within the castrate range and remain suppressed with continuous treatment every 28 days. Bicalutamide "… is a non-steroidal androgen receptor inhibitor. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen."] All patients underwent a planning CT scan in a standardized treatment position an average of 4 days (range, 2-7 days) prior to 3D-CRT initiation. The clinical target volume included the entire prostate and seminal vesicles. The planning target volume included an additional 0.8 to 1 cm margin around the clinical target volume. On the final day of RT, a post-treatment CT scan was also performed in all patients. In addition to clinical measurements, intra-observer variation was assessed by randomly repeated contour determination in 10 patients. Results were provided for two groups of patients: one with 2-3 months' anti-androgen therapy (SNAD) (median 2.7 months) and the other with 3-10 months' anti-androgen therapy (LNAD) (median 4.8 months). For all patients, mean prostate volumes were 49.7 cm^3 (based on the planning CT) and 41.0 cm^3 (based on the post-therapy CT). Results of prostate gland shrinkage were most apparent by the end of three months of anti-androgen treatment. Patients in the LNAD group had significantly smaller prostate gland volume compared to the SNAD group (39.5 cm^3 vs. 60.3 cm^3; p 0.03). In contrast, rectum and bladder volumes did not change significantly between planning and post-treatment CT scans. The authors concluded that when RT planning was performed within 3 months of anti-androgen therapy, a 10-15% reduction in prostate volume was demonstrated following 3D-CRT. This change may have led to increased RT dosage to rectal tissue. The authors suggested the possible need for an additional planning CT to prevent unnecessary radiation exposure in nearby organs.

Shintani et al., 2008

In this prospective study of a case series of 91 patients with tumors of the head and neck of various histological types, the authors studied utility of post-surgical PET/CT prior to adjuvant radiation therapy. Patient characteristics included a median age of 59.6 years, ranging from 35-96 years. Seventy males and 21 females were participants. Tumor types included 62 squamous cell and 29 non–squamous cell cancers. Median time between surgery and postoperative PET/CT was 28 days (range, 13–75 days). Findings suspicious for persistent/recurrent cancer or distant metastasis were biopsied. Correlation was made with changes in patient care. The authors found that, based on PET/CT findings, 24 patients (26.4%) underwent biopsy of suspicious sites, while three patients with suspicious findings did not undergo biopsy because the abnormalities were not easily accessible. Eleven of 24 (45.8%) biopsies were positive for cancer. Treatment was changed for 14/91 (15.4%) patients (11 positive biopsy and 3 nonbiopsied patients) as a result. Treatment changes included abandonment of radiation therapy and switching to palliative chemotherapy or hospice care (4), increasing the radiation therapy dose (6), extending the radiation therapy treatment volume and increasing the dose (1), additional surgery (2), and adding palliative chemotherapy to palliative radiation therapy (1). Treatment for recurrent cancer and primary skin cancer were significant predictors of having a biopsy-proven, treatment-changing positive PET/CT ($p < 0.03$). The authors concluded that despite a number of false positive PET/CT scans in this early postoperative period, PET/CT changed patient management in a relatively large proportion of patients. PET/CT can be recommended in the postoperative, preradiation therapy setting with the understanding that treatment-altering PET/CT findings should be biopsied for confirmation.

Topkan et al., 2008

In this prospective case series of a group of fourteen patients with histologically confirmed, unresectable pancreatic cancer, the authors evaluated CT with co-registered positron emission tomography-computed tomography PET-CT delineating gross tumor volume (GTV). Patients' ages averaged 55 years, ranging from 18 to 70 years of age, and 3 females and 11 males were studied. Ten of the pancreatic tumors affecting the head of the pancreas, while 4 affected the tail. For each patient, two three-dimensional conformal plans were made using the CT and PET-CT fusion data sets. Differences in treatment plans and doses of radiation to primary tumors and critical organs were analyzed. The authors found that changes in GTV delineation were necessary in 5/14 (36%) patients based on PET-CT information. In these patients, the average increase in GTV was 29.7%, due to the incorporation of additional lymph node metastases and extension of the primary tumor beyond that defined by CT. For all patients, the GTVCT versus GTVPET-CT was 92.5 ± 32.3 cm^3 versus 104.5 ± 32.6 cm^3 ($p = 0.009$). However, toxicity analysis revealed no clinically significant differences between two plans with regard to doses to critical organs. The authors concluded that co-registration of PET and CT information in unresectable LAPC may improve the delineation of GTV and theoretically reduce the likelihood of geographic misses.

Zheng et al., 2007

In this prospective study of 39 patients with locally recurrent nasopharyngeal carcinoma (NPC), the authors studied how the addition of FDG-PET/CT influences radiotherapy planning. Eligibility criteria included histologically proven locally recurrent NPC and no evidence of regional or distant metastasis by conventional techniques (including head and neck MRI, SPECT, abdominal ultrasound, chest X-ray, and clinical examination). There were 30 male and 9 female patients in the study group, whose ages ranged from 27-71 years with a median of 48 years. All patients underwent FDG-PET/CT simulation scans. For each patient, the gross tumor volume (GTV) was separately delineated by physicians with or without the addition of PET information and defined as GTV-PET/CT and GTV-CT, respectively. Three-dimensional conformal radiotherapy plans were separately created for PTV-CT and PTV-PET/CT. To assess the potential geographic miss of the PET/CT-based disease in CT-based treatment planning, the size and location of the GTV-PET/CT, PTV-PET/CT, and PTV-CT were analyzed. (The GTV-PET/CT was used as a comparison standard.) The authors found that treatment plans changed from attempted cure to palliation in 4/43 (9%) of patients with the addition of the PET information showing distant metastases. For the remaining 39 patients, the authors concluded that RT coverage of the GTV-PET/CT and PTV-PET/CT by the PTV-CT would be inadequate in 7 (18%) and 20 (51%) patients, respectively. This resulted in <95% of the GTV-PET/CT and PTV-PET/CT receiving at least 95% of the prescribed dose in 4 (10%) and 13 (33%) patients, respectively. Conclusions: The addition of FDG-PET information might influence CT-based radiotherapy planning for locally recurrent nasopharyngeal carcinoma by altering the definition of the target volume, with the potential to avoid a geographic miss of true disease.

<u>Retrospective Case Series Studies:</u>

Cheran et al., 2004

In this retrospective study of 20 patients with biopsy-proven primary lung tumors who had a negative finding on a FDG PET study at the time of diagnosis, the authors reviewed surgical, pathologic, radiographic imaging, and clinical follow-up information were reviewed to confirm the histology, stage, and outcome. These 20 patients included 15 females and 5 males, with ages ranging from 33-77 years (mean, 61 years). Tumor histology included adenocarcinoma (*n* = 7, 35%), bronchioalveolar cell carcinoma (*n* = 6, 30%), carcinoid (*n* = 3, 15%), squamous cell carcinoma (*n* = 2, 10%), otherwise unspecified non–small cell lung cancer (*n* = 1, 5%), and sarcomatoid neoplasm (*n* = 1, 5%). One patient with bronchioalveolar cell carcinoma had multifocal stage IV disease, and all other patients were stage IA (*n* = 14, 70%) or stage IB (*n* = 5, 25%). Eighteen (90%) of the 20 patients underwent curative surgical resection. No patient is known to have tumor recurrence after resection, and three (17%) of the 18 patients are known to be living and free of disease 5 years after surgery. The authors concluded that with the exception of bronchioalveolar cell carcinoma and carcinoid, newly diagnosed lung cancers with negative PET findings are usually early-stage diseases and are associated with a favorable prognosis, suggesting that indeterminate pulmonary nodules, which are PET-negative, can be managed conservatively with serial radiographic studies to monitor for signs of growth. The authors suggested further study to confirm these results with sufficient follow-up in a large cohort of patients with PET-negative lung lesions.

Deniaud-Alexandre et al., 2005

In this retrospective case series study of 101 patients with NSCLC, stages I-III, patients received both CT and FDG-PET imaging, registered based on five fiducial markers. Radiation target delineation was initially performed using CT images, and then FDG-PET images were subsequently used as an overlay to the CT images to define the target volume. In eight patients, FDG-PET revealed undetected distant metastases, making them ineligible for curative radiotherapy. In one patient, combined PET-CT images revealed excessively extensive intrathoracic disease. Of the remaining 91 patients, CT-PET image fusion decreased the gross tumor volume (GTV) in 21 patients and increased GTV in 24 patients. PET images resulted in reduced GTV by at least 25% in seven patients. In some patients, PET-CT images led to better delineation of tumor volume by distinguishing tumor from atelectasis or from mediastinal lymph nodes. The volume of spinal cord receiving at least 45 Gy decreased in two patients. The authors recognized that this study does not include assessment of impact on treatment outcomes from PET-CT integrated images.

Nguyen et al., 2008

In this retrospective clinical review of a series of 50 patients with histologically confirmed anal cancer, the investigators assessed the utility of FDG-PET in anal cancer for staging and impact on radiotherapy planning (RTP), response and detection of recurrent disease. Cases occurred during the period 1996-2006, and included 19 males and 31 females, with median age of 58 years (range 36-85). The clinical impact on management, disease response, recurrence and metastases with CT was compared to that with PET in 48 patients with pre-treatment PET scans. The authors found that the primary anal cancer was strongly FDG avid in 98% of patients with non-excised tumors compared to CT (58%). In addition, pre-treatment PET studies led to upstaging of 8/48 (17%) of patients due to detection of unsuspected pelvic/inguinal nodal disease, and in one additional patient, led to changes in RT plan. The authors noted that "The impact of PET staging on RTP resulted entirely from the identification of additional involved nodal regions in nine patients with clinical N0 (5/28 upstaged) and N2 disease 3/10 upstaged, and 1/10 with more extensive involvement of lymph nodes)". The authors concluded that anal cancer is FDG-PET avid, and that PET upstages in 17% of patients, and changes the RTP in 19% (an additional 2%). The authors also called for further prospective studies.

Grgic et al., 2009

In this retrospective study of 16 consecutive RT candidates with NSCLC, the investigators the relative improvement in fusion quality of combined FDG PET and CT data, using both rigid and non-rigid registration techniques. Patients included twelve men and four women, with a mean age of 65 years, ranging from 45-75 years. Patients were imaged in the RT position for both FDG PET and CT scans, with both scans completed within four to six hours on the same day. Breathing techniques of full inspiration, mid-breath hold, and full expiration were used in each patient. Subsequent fusion of FDG PET and CT scan data was then performed using both rigid and non-rigid algorithms to produce fusion images of the thoracic tumor. To assess the quality of the fusion image, alignment was graded on a scale from 1 (complete lack of alignment) to 5 (exact alignment), by three experienced nuclear medicine physicians, blinded to patient identity or imaging method. Inter-observer agreement of the assessed image quality scores was rated as good (kappa = 0.63 (all anatomic areas), $p < 0.001$). Comparison of average rigid and non-rigid fusion alignment scores indicated improvement using the non-rigid registration algorithm (non-rigid: 3.5 +/- 0.7, rigid: 3.3 +/- 0.7, $p < 0.001$). (A difference in alignment of 5-25 millimeters was scored as 3; a difference of less than 5 mm was scored as 4). Better alignment due to use of the non-rigid algorithm were noted in the lung apices; at the carina; and in the region of the aortic arch. However, there were no significant differences in average alignment scores between rigid and non-rigid registration algorithm results in the area of the tumor. The authors concluded that, with the patient imaged in treatment position, the graded assessment of FDG PET and CT image data alignment quality, in the area of the thoracic tumor, was improved by non-rigid algorithms for image registration, especially if CT imaging is performed during either full inspiration or full expiration.

Soto et al., 2008

In this retrospective study based on a case series of 61 patients with head and neck cancer (HNC) who had failed definitive RT as their sole therapy, the authors studied whether pretreatment FDG-PET-defined biologic target volume (PET-BTV) correlates with the anatomical sites of loco-regional failure (LRF) after RT for head and neck cancer (HNC). The 61 HNC patients were selected from those patients whose squamous cancers originating in mucosa had been definitively but unsuccessfully treated with either 3-D CRT or IMRT (both with no surgery) based on a pre-therapy PET/CT. 95% of patients studied had also been treated with chemotherapy. The GTV and high-risk CTV1 definitions included composite data obtained from diagnostic CT, PET/CT, physical examination, and MRI when available. The median CTV1 dose was 70 Gy. 95% received chemotherapy. For patients with LRF, a recurrence volume (Vr) was identified and was mapped to the pretreatment planning CT and pretreatment PET scan. The authors found that, at a median follow-up of 22 months, 15% (9/61) patients had LRF. For patients with a LRF, 100% (9/9) of failures were inside the GTV. One of nine [11% (95% CI: 3–45%)] had Vr which mapped outside of the pretreatment PETBTV, while 8/9 patients had Vr within the PET-BTV. Predictors of LRF in our series included GTV volume ($p = 0.003$), but not mean SUV ($p = 0.13$) or max SUV ($p = 0.25$). The authors concluded that following treatment in which the GTV was defined based on the composite of imaging and physical examination, the majority, but not all, LRF occurred within the PET-BTV. These results support an important, but not exclusive, role of FDG-PET in defining the GTV.

Thrall et al., 2007

In this retrospective (chart) review study of 39 ovarian cancer patients, the authors studies the use of co-registered FDG PET/CT for surveillance and follow-up of ovarian cancer patients to detect recurrent disease. The 39 ovarian cancer patients (with median age of 53 years, ranging from 31 to 71 years) underwent a total of 59 FDG-PET/CT scans. From chart review, the following information was obtained: clinical indication for FDG-PET/CT, the results of FDG-PET/CT particularly with regard to the additional diagnostic information, the localization of disease and subsequent clinical patient management. The authors found that 24 FDG-PET/CT scans were performed in 22 patients with previously negative or indeterminate CT scans but rising CA-125 levels providing a sensitivity of 90% for localizing disease. Nine FDG-PET/CT in eight patients with clinical symptoms of recurrence but normal CA-125 levels detected all three patients who had recurrent disease confirmed within six months of follow-up. In addition, four FDG-PET/CT performed as routine follow-up with no clinical evidence of recurrent disease were true-negative in all cases. Fourteen FDG-PET/CT in 12 patients with recurrent disease already identified by conventional CT imaging were useful in guiding treatment decisions such as radiation therapy, surgery or chemotherapy by confirming the recurrence and more precisely localizing the site(s) of disease. Notably, FDG-PET/CT helped to avoid surgery in four patients who had additional disease detected in unresectable anatomic areas. A total of 51 FDG-PET/CT were performed in the patients described above with an overall sensitivity and specificity of 94.5% and 100%, respectively. Eight FDG-PET/CT scans in five patients performed for assessment of treatment response following chemotherapy or radiation were useful as the disease was not clearly visualized by conventional CT imaging at baseline. The authors concluded that FDG-PET/CT has the greatest utility in settings of suspected ovarian cancer recurrence, particularly in patients with rising CA-125 levels and negative conventional imaging. FDG-PET/CT was specifically helpful in optimizing the selection of patients for site-specific treatment, including radiation treatment planning, and aided in the selection of optimal surgical candidates. The co-registered metabolic–anatomic information from combined FDG-PET/CT holds promise in replacing the single imaging procedures.

van Loon et al., 2008

In this retrospective study focused on 21 patients for whom either a pre-treatment FDG PET scan and a contrast-enhanced CT scan, or a combined FDG PET-CT scan, was available, the authors investigated the influence of selective irradiation of 18FDG-PET positive mediastinal nodes on radiation fields and normal tissue exposure in limited disease small cell lung cancer (LD-SCLC). For each patient, two three-dimensional conformal treatment plans were made with selective irradiation of involved lymph nodes, based on CT and on PET, respectively. Changes in treatment plans as well as dosimetric factors associated with lung and esophageal toxicity were analyzed and compared. The authors found that FDG-PET information changed the treatment field in 5/21 patients (24%). In 3 patients, this was due to a decrease and in 2 patients to an increase in the number of involved nodal areas. However, there were no significant differences in gross tumor volume (GTV), lung, and esophageal parameters between CT- and PET-based plans. The authors concluded that incorporating FDG-PET information in radiotherapy planning for patients with LD-SCLC changed the treatment plan in 24% of patients compared to CT. Both increases and decreases of the GTV were observed, theoretically leading to either avoidance of geo-graphical miss or decrease of radiation exposure of normal tissues, respectively. The authors mentioned that based on these findings, a phase II trial, evaluating PET-scan based selective nodal irradiation, is ongoing in their department.

Vernon et al., 2009

In this retrospective assessment of 42 patients with head and neck carcinoma (HNC), the authors evaluated clinical outcomes and the predictive value of PET for patients receiving PET/CT-guided definitive radiotherapy with or without chemotherapy. The median age of the patients was 55 years, ranging from 21-81 years of age; 29 males and 13 females participated in the study. All patients received PET/CT imaging with immobilization of the head as part of staging and radiotherapy planning. Radiation doses ranges from 60 to 72 Gy. Data on clinical outcomes including locoregional recurrence, distant metastasis, death, and treatment-related toxicities were collected retrospectively and analyzed for disease-free and overall survival and cumulative incidence of recurrence. The authors found that median follow-up from initiation of treatment was 32 months. Overall survival and disease-free survival were 82.8% and 71.0%, respectively, at 2 years, and 74.1% and 66.9% at 3 years. Of the 42 patients, seven recurrences were identified (three with local recurrence; one with distant metastases, and three with both). Mean time to recurrence was 9.4 months. Cumulative risk of recurrence was 18.7%. The maximum standard uptake volume (SUV) of primary tumor, adenopathy or both on PET did not correlate with recurrence, with mean values of 12.0 for treatment failures vs. 11.7 for all patients. The authors concluded that a high level of disease control combined with favorable toxicity profiles was achieved in this group of HNC patients receiving PET/CT fusion guided radiotherapy with or without plus/minus chemotherapy. They also suggested the value of further large-scale clinical studies.

Waaijer et al., 2003

In this retrospective ('pilot') study of 13 cases with primary oropharyngeal squamous cell carcinoma, treated with RT with curative intent, and with diagnostic (CT1) and then RT planning (CT2) CT scans (in treatment position) performed at the study institution, the authors studied the difference in tumor volume between the initial and RT planning CT, as well as the clinical consequences of time elapsed between CT1 and CT2 using a tumor control probability (TCP) model. Patients (10 men, three women) ranged in age from 47-102 years, with an average age of 68 years. Two, four and seven tumors were Stage II, III, and IV, respectively, based on CT1 results. Tumor volume changes were calculated using a sum of areas technique based on assessment by a resident and two experienced radiation oncologists. Waiting time was defined as the difference in time between histopathological diagnosis and initiation of radiation therapy. The results showed that the average waiting time was 56 days, ranging from 45 – 69 days). The tumor doubling time ranged from 21 to 256 days. In nine of 13 cases, the waiting time was at least one doubling time in duration; in four of those cases, it was two doubling times. Tumor volumes calculated from CT scans increased, on average among these patients, by 70%, and disease progression (based on a change of at least one Stage) occurred in 9/13 patients. Based on the TCP model, the likelihood of tumor control decreased among individual patients from an average of 66% to 47%.

Case Series Studies (unknown whether prospective or retrospective)

Esthappan et al., 2008

In this case series of ten patients with cervical cancer and positive para-aortic lymph nodes (PALN), the authors reviewed the results of using positron emission tomography (PET)/computed tomography (CT) to guide intensity-modulated radiation therapy (IMRT). Patient demographic information was not included. Immediately after integrated PET/CT scanning, a second CT scan was performed for radiation treatment planning. Treatment plans were generated to deliver 60.0 Gy to the PET-positive PALN and 50.0 Gy to the PALN and pelvic lymph node beds, with plans optimized to deliver at least 95% of the prescribed doses to at least 95% of each target volume. Dose–volume histograms were calculated for normal structures (bowel and kidney) based on radiation plans. The plans of 10 patients were reviewed. Target coverage goals were satisfied in all plans. Analysis of dose–volume histograms indicated that treatment plans involved irradiation of approximately 50% of the bowel volume to at least 25.0 Gy, with less than 10% receiving at least 50.0 Gy and less than 1% receiving at least 60.0. With regard to kidney sparing, approximately 50% of the kidney volume received at least 16.0 Gy, less than 5% received at least 50.0 Gy, and less than 1% received at least 60.0 Gy. The authors commented that their guidelines for the evaluation of target coverage and normal tissue sparing should facilitate the more aggressive radiation treatment of cervical cancer.

Girinsky et al., 2007

The authors indicated that the purpose of this study of RT planning in 30 patients with Hodgkin lymphoma was to answer questions about the biological significance of FDG-PET positive areas, especially as applied to customized RT following chemotherapy for each patient. Patients with early-stage Hodgkin lymphoma received three to six cycles of ABVD (doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine) chemotherapy. In two patients, FDG-PET findings indicated advanced-stage disease, and these two patients received eight cycles of ABVD. FDG-PET scans were performed for all patients before and after chemotherapy. All patients had a CT simulation for treatment planning. The CT simulation was coregistered with the prechemotherapy CT and FDG-PET scan. All prechemotherapy volumes were superimposed on the CT simulation. The initially involved lymph node areas to be irradiated were delineated on the CT simulation scan. Chemotherapy -induced shrinkage rates of the tumor masses visible on CT scan and on FDG-PET were determined and compared. Before chemotherapy, FDG-PET-avid areas represented 25% of the total volume on CT. After chemotherapy, the influence of initial FDG-PET data on the delineation of involved-node radiotherapy fields was significant and was due to the fact that in 36% of the patients, FDG-PET helped pinpoint lymph nodes that were undetected on CT. After chemotherapy, the rates of tumor volume shrinkage on CT and FDG-PET were similar. This finding suggests similar chemosensitivity for FDG-PET-avid and non-avid areas. There was no correlation between initial FDG-PET-avid volumes and the clinical outcome. The authors concluded that prechemotherapy FDG-PET data are essential for correctly implementing the involved-node radiotherapy concept but seem to be of minimal value for applying the concept of dose painting.

Hwang et al., 2009

In this study of 12 patients treated with external beam RT for head-and-neck cancer, the authors investigated how much uncertainty was associated with incorporating diagnostic PET/CT and PET into the RT planning process. Accuracy of registration of normal structures, and of tumors was assessed using an overlap index (normal structures and tumors) and with differences in the center-of-mass (COM) positions (tumors only). Manual and automated methods, based on fixed or deformable models, were used for registration. PET/CTs and treatment-planning CTs from all patients were used to evaluate image registration accuracy. The PET/CTs also were used without the contemporaneously acquired CTs to evaluate the registration accuracy of stand-alone PET. The authors reported that registration accuracy was better with PET/CT than with PET alone. The COM displacements ranged from 3.2 ± 0.6 mm (mean ± 95% confidence interval, for brain) to 8.4 ± 2.6 mm (spinal cord) for registration with PET/CT data, compared with 4.8 ± 1.7mm(brain) and 9.9 ± 3.1mm(spinal cord) with PET alone. Deformable registration improved accuracy, with minimum and maximum errors of 1.1 ± 0.8 mm (brain) and 5.4 ± 1.4 mm (mandible), respectively. The authors concluded that PET and/or PET/CT image data acquired in diagnostic positions can be incorporated into the treatment planning process through the use of advanced image registration algorithms, but precautions must be taken, particularly when delineating tumor volumes in the neck. The authors commented that acquisition of PET/CT in the treatment-planning position would be the ideal method to minimize registration errors.

Ireland et al., 2007

This small study (n=5) investigated the effect of positioning (diagnostic vs. treatment) positioning of use of PET/CT images for RT planning, using both rigid and non-rigid image registration, compared to RT planning CT. The authors noted that acquiring PET/CT in treatment position is problematic, and in practice for some patients it may be beneficial to use diagnostic PET/CT for radiotherapy planning. A second aim of this study was to assess whether PET/CT acquired in diagnostic position can be registered to planning CT. Five patients with head and neck cancers who underwent both PET/CT and conventional CT for radical radiotherapy planning were included. Four independent observers assessed the registration of both PET/CT and planning CT, using rigid and non-rigid image registration, based on a set of anatomic landmarks. The root-mean-squared errors (in millimeters) were calculated. The investigators found that non-rigid and rigid registration errors for treatment position PET/CT to planning CT were 2.77 +/- 0.80 mm and 4.96 +/- 2.38 mm, respectively (p = 0.001 by paired t test). Applying the non-rigid registration to diagnostic position PET/CT produced a more accurate match to the planning CT than rigid registration of treatment position PET/CT (3.20 - 1.22 mm and 4.96 - 2.38 mm, respectively, p = 0.012). The authors concluded that non-rigid registration provided a more accurate registration of head and neck PET/CT to treatment planning CT than did rigid registration. They also concluded that non-rigid registration of PET/CT acquired with patients in a standardized, diagnostic position can provide images registered to planning CT with greater accuracy than a rigid registration of PET/CT images acquired in treatment position. The authors suggested that this finding may allow greater flexibility in the timing of PET/CT for head and neck cancer patients due to undergo radiotherapy.

Jensen et al., 2007

In this study of 61 patients with squamous-cell carcinoma of the head and neck (SCCHN) who underwent both a diagnostic and a treatment planning scan, and who were treated with radiotherapy, the authors investigated the effect of waiting-time (prior to radiotherapy) CCHN). These 61 patients were available for analysis from a consecutive series of 648 patients were seen, and 414 treated with primary radiotherapy; 95 had two scans and 61 sets were eligible for comparison. Among the 61 patients, 47 were men, and 14 were women. For 45 patients the measured volume was primary tumor and lymph node metastases and for 16 patients where tumor bed was not measurable, the measured volumes were from lymph node metastasis only. Endpoints were change in tumor volume, tumor volume doubling time (TVD) and disease progression measured by TNM-classification and RECIST criteria. The authors found that the median interval between eligible scans was 28 (5–95) days. 38/61 (62%) patients had measurable increase in tumor volume, median 46% (6–495%). There was an association of waiting time to tumor volume increase: the authors found that "… among patients with an interval of 2 weeks or less 4/12 patients (33%) showed significant progression (33%), for the interval of 2–4 weeks 13 of 19 patients showed measurable progression (68%) and a similar frequency of 70% (21/30) was found for patients with more than 4 weeks' interval between scans. The median tumor volume doubling time (TVD) for all patients was 99 (range: 15 - > 234) days, but for the half of patients with fastest growing tumors median TVD was 30 (range: 15–41) days. TVD was also affected by histological differentiation. After therapy, twelve of 61 patients (20%) developed new lymph-node metastasis and 10/61 (16%) progressed in TNM-classification. Evaluated by RECIST criteria, 18 (30%) patients had progressive disease. The authors concluded that there was a negative impact of waiting time in patients with SCCHN. Within an average time of 4 weeks the majority of the patients developed significant signs of tumor progression. The authors commented that it was not possible to define a threshold for acceptable time intervals in order to avoid volume changes, or to define a subgroup that has no negative impact of delay.

Klopp et al., 2007

In this study, the authors investigated whether the RT target would be better defined by PET/CT compared with CT alone. Patterns of treatment failure were assessed in 35 patients with NSCLC whose treatment was based on a PET-defined radiotherapy target. Effects of standardized uptake value (SUV) on recurrence after radiotherapy were also studied. The PET/CT scans were obtained with patients in the treatment position with custom immobilization for use in radiation treatment planning. Nine to 11 regions of interest (ROIs) were identified for each patient, including the primary tumor and regional nodes. Maximum SUV, volume, and mean dose received were recorded for each ROI, and follow-up scans were used to evaluate for recurrence in each ROI. 353 ROIs were identified from 35 patients. 5.7% of patients developed isolated out-of-field recurrences. Recursive partitioning analysis was used to divide ROIs into low, intermediate, and high risk by using volume and SUV. All low-risk ROIs with volumes less than 1.2 cm^3 were recurrence free compared with 73% of intermediate-risk ROIs (volume > 1.2 cm^3; SUV < 13.8) and 29% of high-risk ROIs (SUV > 13.8). The authors concluded that limiting the target volume to predominantly PET-positive disease resulted in a low rate of isolated out-of-field recurrences. The SUV and volume were predictors of recurrence. Recursive partitioning analysis identified SUVs greater than 13.8 as the best identifier of ROIs at the greatest risk of recurrence; control rates for this subgroup did not show a dose–response relationship within the range of doses administered.

Paulino et al., 2005

In this study, the authors investigated the effect of using FDG PET with that of CT for determining gross tumor volume (GTV) and the differences in volume and dose coverage of the PET-GTV when the CT-GTV is used for radiotherapy planning. A consecutive case series of 40 patients (32 males, 8 females, with median age of 56 years, ranging from 32-75 years) with intact squamous cell carcinoma arising in the head-and-neck region underwent intensity-modulated radiotherapy (IMRT). All patients underwent CT simulation for treatment planning followed by PET-CT in the treatment position. CT simulation images were fused to the CT component of the PET-CT images. The GTV using the CT simulation images were contoured (CT-GTV), as was the GTV based on the PET scan (PET-GTV). The IMRT plans were obtained using the CT-GTV. The authors found that PET-GTV was: smaller than CT-GTV in 30 cases (75% of patients); the same size in 3 (8%); and larger in 7 (18%) cases. The median PET-GTV and CT-GTV volumes were 20.3 cm^3 (range, 0.2–294) and 37.2 cm^3 (range, 2–456), respectively. The volume of PET-GTV receiving at least 95% of the prescribed dose was 100% in 20 (50%), 95–99% in 10 (25%), 90–94% in 3 (8%), 85–89% in 1 (3%), 80–84% in 2 (5%), 75–79% in 1 (3%), and <75% in 3 (8%) cases. The minimal dose received by 95% of the PET-GTV was >100% in 19 (48%), 95–99% in 11 (28%), 90–94% in 5 (13%), 85–89% in 2 (5%), and <75% in 3 (8%) cases. The authors concluded that PET-GTV was larger than the CT-GTV in 18% of cases. In approximately 25% of patients with intact head-and-neck cancer treated using IMRT, the volume of PET-GTV receiving at least 95% of the prescribed dose and minimal dose received by 95% of the PET-GTV were less than optimal.

Schwartz et al., 2005

In this ‘proof of concept’ study, based on a group of twenty patients with squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx , the authors examined the use of registered FDG-PET/CT imaging to guide head and neck intensity modulated radiotherapy (IMRT) planning. All patients underwent FDG-PET and contrast-enhanced CT imaging of the head and neck before neck dissection surgery. Combined FDG-PET/CT images were created by use of a nonrigid image registration algorithm. All IMRT plans were theoretical and were not used for treatment. We prescribed 66 Gy in 30 fractions to FDG-avid CT abnormalities and nodal zones directly involved with disease, without prophylactic coverage of uninvolved neck levels. Matched CT-guided IMRT plans designed according to the specifications of Radiation Therapy Oncology Group (RTOG) H-0022 were available for comparison. In addition, the authors investigated the feasibility of FDG-PET/CT – directed IMRT dose escalation in five patients with FDG-avid disease located away from critical normal structures. After 66 Gy, FDG-avid disease with 0.5-cm margins was boosted in 220 cGy increments until dose-limiting criteria were reached. The authors found that elimination of prophylactic coverage to FDG-PET/CT – negative neck levels markedly reduced mean dose (Dmean) to the contralateral parotid gland ($p < .001$) and Dmean to the laryngeal cartilage ($p = .001$). No FDG-PET/CT– directed plan missed pathologically verified nodal disease. During the dose escalation exercise, the dose was successfully increased to 95% of the planning target volume (PTV95%) to a mean of 7490 cGy (range, 7153–8098 cGy). The authors concluded that these results showed ‘early proof of the principle’ that FDG-PET/CT–guided IMRT planning can selectively target and intensify treatment of head and neck disease while reducing critical normal tissue doses. The authors suggest that routine clinical use of such planning should not be attempted until the accuracy of FDG-PET/CT is fully validated. Future directions, including refinement of treatment to gross disease and radiologically uninvolved neck nodal levels, are discussed.

Vesprini et al., 2008

In this study of ten patients with gastro-esophageal cancers, the authors evaluated the effect of adding fused positron emission tomography/computed tomography (PET/CT) imaging compared with CT alone in the identification of the gross tumour volume (GTV) for radiation therapy. Patients included 7 males and 3 females, and tumors included 4 squamous cell carcinomas, 5 adenocarcinomas, and one mixed adeno-squamous carcinoma. Eight tumors were in the lower third of the esophagus or at the GE junction; 2 were in the middle third of the esophagus. Image sets were anonymised and co-registered. Six radiation oncologists independently defined the GTV, first using the CT data alone supplemented by standardized clinical and diagnostic imaging information, and second using PET/CT data. The standard deviation for both GTV length and volume (excluding involved lymph nodes) was taken as a measurement of inter-observer and intra-observer variability. Computer software that calculates volume overlap between contours was also used to generate an observer agreement index to compare intra- and inter-observer variability. The authors found that adding FDG-PET imaging decreased the median standard deviation for tumour length from 10 mm (range 8.1 - 33.3, mean 12.4 mm) for computed tomography alone to 8 mm (range 4.4 - 18.1, mean 8.1 mm) for PET/CT (P=0.02). Eight of the 10 patients showed an increase in volume of overlap between observers with the addition of FDG-PET imaging to the contouring process (P=0.05). The average observer agreement index in PET/CT was 72.7% compared with 69.1% when using computed tomography alone. There was significantly less intra-observer variability in all measures when PET/CT was used. The median standard deviation in length improved from 5.3 to 1.8 mm, the median standard deviation in volume improved from 4.5 to 3 cm3 and the median observer agreement index improved from 76.2 to 78.7% when computed tomography alone was compared with PET/CT. The corresponding P values were 0.001, 0.033 and 0.022, respectively. The authors concluded that adding FDG-PET to computed tomography-based planning for the determination of primary tumour GTV in patients with gastro-esophageal carcinoma decreases both inter-observer and intra-observer variability.

Wang et al., 2006

In this study, a group of 28 patients (19 males, 9 females, median age 52, range 21-81 years) with head and neck carcinomas and various stages (T1-T4a, N0-N3) who had not had surgical resection of their primary disease underwent FDG-PET/CT fusion-guided IMRT. Initial clinical outcomes of these patients were reported. During the treatment-planning FDG-PET/CT scan, patients were immobilized with face masks including five fiducial markers. FDG -PET and planning CT scans were performed on the same flattop table in one session and were then fused. Target volumes and critical organs were contoured, and IMRT plans were generated based on the fused images. The authors found that all 28 patients had abnormal increased uptake in FDG-PET/CT scans. PET/CT resulted in CT-based staging changes in 16 of 28 (57%) patients. In those 16 patients, volume differences between the CT-based gross target volumes and the PET/CT based gross target volumes (all contoured by two radiation oncologists) ranged -24.8 to +45.6 cm^3, or from approximately -40 to 40 %. These volume differences were described by the authors as 'significantly different' (that is, the absolute values of the difference exceeded approximately 1%) in 14 of 16 (88%) patients. In addition, 16 of 28 patients who were followed for more than 6 months did not have any evidence of locoregional recurrence in the median time of 17 months. Authors concluded that fused PET/CT images were found to be useful to delineate GTV required in IMRT planning. PET/CT should be considered for both initial staging and treatment planning in patients with head-and-neck carcinoma.

Yildirim et al., 2008

In this study, sixteen patients with locally advanced (FIGO stage IIB–IVA) cervical squamous cancer (LACC) patients with negative conventional CT findings were studied to evaluate the usefulness of integrated PET/CT for the detection of para-aortic nodal status and to test whether PET/CT change management strategy with negative conventional CT findings. The median patient age was 48.7 (range 42–67) years. All patients underwent firstly PET/CT scans then extraperitoneal surgical exploration for para-aortic lymphadenectomy. Based on histopathological confirmation, the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the PET/CT for para-aortic lymph node metastasis were estimated. The authors found that the accuracy, sensitivity, specificity, PPV and NPV of the PET/CT were 75%, 50%, 83.3%, 50% and 83.3%, respectively. As a consequence of PET/CT evidence of involvement of pelvic lymph nodes, extended field radiation therapy (EFRT) was used instead of pelvic RT in four of sixteen (25%) patients, in combination with cisplatin chemotherapy. The authors concluded that, despite the small study group size, results suggested the value of PET/CT as an effective imaging technique in the evaluation of LACC with negative CT findings. One of its advantages may be for management of radiation fields for therapy.

4. MEDCAC

CMS did not convene the MEDCAC for this reconsideration.

5. Evidence Based Guidelines

The National Comprehensive Cancer Network (NCCN) Practice Guidelines (NCCN 2009) address the uses of FDG PET for RT planning in special situations. Several examples of guideline recommendations are presented in this section concerning: RT planning. The first example, on p. 3 of 7 of the NCCN Clinical Practice Guideline for Non-Small Cell Lung Cancer V.2.2010 (accessed on 3/15/2010 at www.nccn.org), the NCCN guideline panel indicated that

" … Treatment planning should be performed by CT scans obtained in the treatment position. IV contrast should be used for better target delineation whenever possible, especially in patients with central tumors or with nodal disease. PET-CT is preferable in cases patients with significant atelectasis and when IV contrast is contraindicated. PET-CT can significantly improved target accuracy.(ref. 33) "

Reference 33 in that NCCN Clinical Practice Guideline refers to MacManus 2009.

As another example, the 2010 NCCN Clinical Practice Guideline for Cervical Cancer (V.1.2010, accessed on 4/6/2010 at www.nccn.org) suggests that:

" … [U]se of 3-dimensional treatment planning for both the external beam RT fields and the brachytherapy placements may assist in customized shaping of dose distributions to ensure adequate tumor coverage in all dimensions and to minimize normal tissue exposure."

However, this guideline does not indicate the need for RT planning FDG PET scans with the patient in the treatment position.

As a final example, the 2010 NCCN Clinical Practice Guideline for Head and Neck Cancer (V.1.2010, accessed on 4/6/2010 at www.nccn.org) indicates generally that:

"Radiation therapy for (head and neck) cancer is extremely complex. … Much variation in practice exists among many countries and even within various institutions in the same country".

This guideline does not explicitly recommending patient position and image registration approaches for the RT planning process, citing only the diversity in RT planning as currently practiced.

6. Professional Society Position Statements

In addition to the requestors' original letter of October 14, 2009, a further statement was sent to CMS on December 9, 2009, by Drs. McCarthy, Harolds, Neiman, Graham, and Ms. Thevenot on behalf of their respective professional organizations. Their public comment of December 9, 2009 included the following:

"We would also like to bring to the attention of CMS two additional recent publications that provide further support for easing the single-scan restriction.

"Kidd et al. (2009) [1] evaluated a cohort of patients with locally advanced cervical cancer treated with brachytherapy and intensity-modulated radiation therapy (IMRT), in which the IMRT was guided by the results of FDG-PET. The PET studies in these patients were performed as repeat examinations, after an earlier initial staging study, so that the PET data could be acquired in the treatment position and thus properly fused with the simulation CT for planning of the IMRT. By comparison with a historical control group of similar patients treated with brachytherapy and conventional external radiation, the patients who underwent PET-guided IMRT had better overall and cause-specific survival and less treatment-related toxicity. This study provides important evidence that FDG-PET used for radiation treatment planning leads not only to altered treatment plans, but also to actual improvement in patient outcomes. As we noted in our original request, there is broad consensus that FDG-PET to be used for this purpose must be obtained in the treatment position, and this will generally require a separate study from the one performed for initial staging of the patient's tumor burden.

"Simpson et al. (2009) [2] conducted a survey of a random sample of 1,600 radiation oncologists regarding their utilization of advanced imaging technologies for target delineation in radiation therapy, and their future plans for such use. [3] The study found that 95% of the responding physicians, reported using advanced imaging technology for target delineation, and that FDG-PET was the most common technology employed (by 76% of respondents). The most common cancers treated using image-guided target delineation were lung (83%), central nervous system (79%), and head and neck (79%). Finally, among users of advanced imaging technologies, 66% planned to increase use of such technologies, while 30% of nonusers planned to adopt these technologies in the future. This study indicates the significant expansion of the use of FDG-PET for target delineation over the past decade, and suggests that oncologists find such imaging to have clinical value.

"In conclusion, we continue to believe that the strict one-scan limitation cannot be reconciled with either the prevailing standard of care or the existing literature, and therefore encourage CMS to amend CAG-00181R to accommodate and cover clinically necessary "second initial" scans in situations such as those described in our reconsideration request. Such a policy would harmonize the omnibus PET coverage policy with the existing evidence on the clinical value of certain 'second initial treatment strategy evaluation' scans.

"As we noted in our reconsideration request, we remain cognizant of the desire of CMS to avoid situations in which limited coverage of second initial scans could lead to attempts to obtain reimbursement improperly for second initial scans beyond such circumstances. However, we believe that it is possible to extend coverage for certain limited radiation therapy purposes and in the other scenarios we describe without allowing the exception to consume the general rule."

CMS has reviewed (please see above) the prospective case-control article cited in this public comment (Kidd et al., 2009). The other citation (Simpson et al., 2009) describes the result of a survey of radiation oncologists in the United States and is not further reviewed as evidence (i.e., data concerning the benefit in terms of patient outcomes, based on clinical studies of actual patient experience) given CMS standards for evidence review.

7. Expert Opinion

Except for the public comments from a number of radiation oncologists, nuclear medicine physicians, radiologists, and other experts, whose comments are summarized below, CMS did not receive expert opinion on the proposed decision.

8. Public Comments

Initial Comment Period: November 9, 2009 through December 9, 2009

CMS received thirty-five public comments during the initial comment period.

Comments were received from medical and surgical oncologists, nuclear medicine physicians, general radiologists, professors of medicine at various university hospitals, FDG PET facilities and other sources. Additional evidence citations submitted in public comments were reviewed above.

Eighteen comments supported the request to expand coverage based on the need to perform any additional FDG PET scan for initial treatment planning. Of these eighteen, 2 also supported expanding coverage based on an initial false negative FDG PET scans subsequently found to be cancer via diagnostic testing at a later date. Two other commenters supported coverage for any additional FDG PET scan for initial treatment planning in the situation of delayed initial treatment. In contrast, one commenter (a health insurance organization) did not support the request on the grounds of insufficient evidence of improvement of health outcomes:

"In regards to the current open NCA tracking sheet on PET for the initial treatment strategy for solid tumors and myeloma, our members have raised questions pertaining to coverage for multiple studies at the initial stage of treatment. Reliable and rigorous evidence is needed to determine whether the additional use of this technology improves patient outcomes for each solid tumor type and myeloma and provider's treatment decisions. PET studies are often associated with false positives and negatives, as well as potential harm of additional exposure to radiation, and therefore should be utilized only when there is demonstrated clinical need.

"Our members do not support providing coverage for more than one PET scan for solid tumors or myeloma without sufficient evidence that a second test is necessary to make treatment decisions and that these decisions improve health outcomes."

Public commenters suggested six citations, of which CMS reviewed four as full text articles: Cheran et al., 2004; Kidd et al., 2009; Jensen et al., 2007; and Waaijer et al., 2003 (please see above). Two other citations, not considered relevant as evidence for further review in this decision memo, were Salama et al., 2009 and Simpson et al., 2009 that either summarized expert opinion or surveyed current practice patterns of radiation oncologists.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A) of the Social Security Act. This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment.

The Medicare regulations at 42 CFR § 410.32(a) state in part, that "…diagnostic tests must be ordered by the physician who is treating the beneficiary, that is, the physician who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem." Thus, we looked for evidence demonstrating how the treating physician uses the result of any additional FDG PET scan for initial treatment planning .

We considered the evidence in the hierarchical framework of Fryback and Thornbury (1991) where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. We believe that evidence of improved health outcomes is more persuasive than evidence of test characteristics.

In evaluating diagnostic tests, Mol and colleagues (2003) reported: "Whether or not patients are better off from undergoing a diagnostic test will depend on how test information is used to guide subsequent decisions on starting, stopping, or modifying treatment. Consequently, the practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes." When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

Medicare already grants broad coverage for certain oncologic uses of FDG PET to guide initial management leading to definitive first line therapy. The current NCD does not prohibit coverage for the indications of interest in this reconsideration. We are considering whether *any additional FDG PET scan for initial treatment planning* is reasonable and necessary, and if so, under what conditions. The requestors describe various scenarios under which factors specific to an individual beneficiary, e.g. concomitant illness or patient indecision, could lead a treating physician to recommend redoing the "initial" diagnostic workup. They also suggest that an FDG PET scan done as part of the initial workup may be inadequate for a more specialized need, i.e. RT planning. We agree that the requesters have identified some situations where any additional FDG PET scan for initial treatment planning would be necessary. We are modifying the NCD to permit the potential for any additional FDG PET scan for initial treatment planning for such situations. However, because the evidence is not currently adequate to identify all such situations as a matter of a nation-wide policy, we will enable local Medicare contractors to make the reasonable and necessary determination for any additional FDG PET scan for initial treatment planning based on an evaluation of a patient’s particular medical circumstances.

As a diagnostic test, FDG PET would not be expected to directly change health outcomes, i.e. there is no evidence that administration of FDG is, in and of itself, therapeutic. Rather, a diagnostic test, including FDG PET, affects health outcomes through changes in disease management brought about by a physician’s actions taken in response to test results. Such actions may include decisions to treat or withhold treatment, to choose one treatment modality over another, or to choose a different dose or duration of the same treatment. To some extent the usefulness of a test result is constrained by the available management alternatives.

Questions

a. *Is the evidence adequate to conclude that the use of subsequent FDG PET scans for radiation therapy planning will meaningfully alter the recommended treatment strategy for beneficiaries who have a diagnosis of solid tumors or multiple myeloma?*
b. *Is the evidence adequate to conclude that the use of subsequent FDG PET scans for radiation therapy planning will meaningfully alter health outcomes for*
c. *beneficiaries who have a diagnosis of solid tumors or multiple myeloma?*

Successful radiotherapy for cancer is based on delivery of sufficient radiation dose within the space occupied by tumor in order to control the malignancy, while minimizing radiation to adjacent uninvolved tissue to avoid its toxic effects. The asserted primary value of any additional FDG PET scan for initial treatment planning is to more accurately define the spatial extent (in three dimensions) of the intended radiation target while sparing non-targeted tissue. Such unwanted spillover of radiation into uninvolved tissue may be a source of late-term complications, negating any benefit in tumor control. Such concerns have been noted in other uses of computerized tomography, e.g., diagnostic cardiac vascular imaging and in evaluating head trauma, and are attracting increasing attention related to unnecessary radiation exposure.

In a number of the citations reviewed (including Facey et al., 2007; Kidd et al., 2009; Anderson et al., 2007; De Ruysscher et al., 2005; De Ruysscher et al., 2005B; Ford et al., 2008; Gillham et al., 2008; Hentschel et al., 2008; Hutchings et al., 2007; Kruser et al., 2009; Onal et al., 2009; Shintani et al., 2008; Topkan et al., 2008; Zheng et al., 2007; Girinsky et al., 2007; Nguyen et al., 2008, and Van Loon et al., 2008), evidence based on clinical studies such as prospective case-control studies or case series supported the impact of either actual or expected changes in RT administration or on treatment strategy because of results of any additional FDG PET scan for initial treatment planning . Such changes in target position and volume are unpredictable in an individual patient. Clinical meaningful changes in tumor volume or stage, which could affect RT planning, may occur after the initial FDG PET scan for staging, potentially as early as several weeks after (Waaijer et al., 2003).

The published evidence reviewed (as listed above) indicates a variety of reasons for changes in the location or size of the RT target on any additional FDG PET scan for initial treatment planning : performance of the scan with the patient in treatment position rather than in staging position; changes in other technical factors; intercurrent treatment effects, including surgery, chemotherapy, and hormone manipulations; tumor growth and/or spread; and selection of different parameters or algorithms for RT planning.

Among the cited articles, a number expressed the concern that by using results of any additional FDG PET scan for initial treatment planning, undesirable irradiation of adjacent normal tissue can be minimized. Much of the evidence for this was from comparisons of estimate radiation doses delivered to adjacent tissues (examples of such studies include De Ruysscher et al., 2005 and Gillham et al., 2008).

Ideally (from the standpoint of coverage decision-making), evidence about the clinical effect of any additional FDG PET scan for initial treatment planning would show benefits in healthcare outcomes compared to similar patients in whom any additional FDG PET scan for initial treatment planning was not performed. However, as noted in the Facey et al., 2007 evidence review, such findings about improved healthcare outcomes is limited. In CMS review of published studies, some suggested by public commenters, included several such studies of outcomes. As one example, Kidd et al., 2009 studied outcomes of FDG PET-guided IMRT in patients with cervical cancer, and found better overall survival and significantly lower risk of significant bladder or bowel complications. Another example, the De Ruysscher et al., 2005B study, FDG PET-guided mediastinal irradiation was associated with better local control of NSCLC; however, these results were uncontrolled and generally lacked biopsy confirmation of local or distant failure. The current base of published evidence from clinical studies about the benefit of any additional FDG PET scan for initial treatment planning is based predominantly on studies demonstrating changes in RT management or, less often, on studies demonstrating changes in treatment strategy (from intended cure to palliation) due to detection of distant metastases, undetected at the time of initial staging studies.

In the future, we hope that additional clinical studies would focus on indicators of outcomes such as better local tumor control and longer patient survival. In a few studies, such as Deniaud-Alexandre et al., 2005, the simulated effect of such volume/position changes on RT dose delivery to adjacent organs, guided by any additional FDG PET scan for initial treatment planning suggests patient benefit due to decreased harm through reduced ‘bystander’ organ radiotoxicity. We encourage additional follow-up comparative studies focusing on subsequent indices of organ damage or function.

We note that while promising, outcome studies due to >any additional FDG PET scan for initial treatment planning , as exemplified by the Kidd et al., 2009 study, should recognize the inherent limitations of using historical controls and of relatively short followup period of the treated group compared with that of historical controls.

To summarize, as we consider the request and study the limited evidence for clear healthcare outcome improvement, we do not believe that a broadly generalizable NCD granting coverage for >any additional FDG PET scan for initial treatment planning is supportable at this time. However, we nevertheless recognize that idiosyncratic issues may arise during the course of anti-cancer evaluation and treatment, leading to potential delays in anticancer treatment of beneficiaries. The impact of any specific event, e.g. the discovery of coronary artery disease or an infection, on anticancer treatment will depend on factors such as the overall health of the patient and the urgency of his or her condition and must be considered unpredictable.

Nevertheless, CMS believes that the base of published evidence reviewed above (and in the prior NCD CAG-00181R) is adequate to support the elimination of the coverage restriction on initial anticancer treatment strategy to one FDG PET scan. Accordingly, CMS proposes to modify the NCD so that coverage continues to be provided nationally for one initial FDG PET for RT planning. In addition, local Medicare contractors may make reasonable and necessary determinations with regard to coverage of >any additional FDG PET scan for initial treatment planning. For any individual beneficiary the usefulness of any additional FDG PET scan for initial treatment planning may be affected by the beneficiary's specific medical problem, the availability of results of other diagnostic tests and the expertise of the interpreting physician. We believe that for such an individual situation, our local administrative contractors, who may more readily obtain this information, can make these determinations within their jurisdictions.

Health Disparities

In our evidence review, CMS did not identify minority subgroup data related to any additional FDG PET scan for initial treatment planning in the Medicare beneficiary population. CMS encourages the scientific community to collect these data.

IX. Conclusion

The Centers for Medicare and Medicaid Services (CMS) was asked to reconsider the April 3, 2009 NCD provision at Section 220.6.17 of the National Coverage Determinations (NCD) Manual, described below, that established an absolute frequency limitation of only one FDG PET study for the noted purposes.

"CMS will cover only one FDG PET study for beneficiaries who have solid tumors that are biopsy proven or strongly suspected based on other diagnostic testing when the beneficiary's treating physician determines that the FDG PET study is needed to determine the location and/or extent of the tumor for the following therapeutic purposes related to the initial treatment strategy:

- To determine whether or not the beneficiary is an appropriate candidate for an invasive diagnostic or therapeutic procedure; or
- To determine the optimal anatomic location for an invasive procedure; or
- To determine the anatomic extent of tumor when the recommended anti-tumor treatment reasonably depends on the extent of the tumor."

After careful review, CMS believes that the current absolute restriction is not supported by the available evidence and therefore proposes to amend 220.6.17 of the National Coverage Determinations Manual:

1. the NCD will be changed to remove the current absolute restriction of coverage to 'only one' FDG PET scan to determine the location and/or extent of the tumor for the therapeutic purposes related to the initial treatment strategy as described above;
2. CMS will continue to nationally cover one FDG PET scan to determine the location and/or extent of the tumor for the therapeutic purposes related to the initial treatment strategy as described above; and
3. local Medicare administrative contractors will have discretion to cover (or not cover) within their jurisdictions any additional FDG PET scan for the therapeutic purposes related to the initial treatment strategy as described above.

For any individual beneficiary the usefulness of any additional FDG PET scan for initial treatment planning might be affected by the beneficiary's specific medical problem, the availability of results of other diagnostic tests and the expertise of the interpreting physician. We believe in such situations that our local administrative contractors, who may more readily obtain this information, can make these determinations about any additional FDG PET scan for initial treatment planning within their jurisdictions. We do not believe that a national coverage determination is the most appropriate way to address coverage for any additional FDG PET scans for the therapeutic purposes related to the initial treatment strategy at this time.

We are requesting public comments on this proposed decision memorandum pursuant to §1862(l)(3) of the Social Security Act (hereinafter, the Act). We are particularly interested in comments that include new evidence we have not reviewed here or in past considerations of this NCD. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

APPENDIX A

General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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